REMARKS

In this amendment, claim 29 has been amended to recite "said container is metal and is provided with an inert non-metal interior surface." Support for the amendment can be found throughout the specification, for example, at page 4, line 14 to page 5, line 4, and page 9, line 5 to page 10, line 29. Thus, the amendment is fully supported by the specification. Claims 1-28 and 38-48 have been previously cancelled without prejudice or disclaimer. Therefore, claims 29-37 remain pending.

35 U.S.C. § 102

Claims 29 and 31 are rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by Blondino et al. (U.S. Patent No. 6,290,930). The Office alleges that Blondino et al. discloses a stabilized medicinal aerosol solution formulations adapted for use in a pressurized aerosol container. The Office further alleges that the aerosol formulation comprises budesonide, at least one fluoroalkane propellant and a co-solvent, and that it is filled in a plastic coated glass bottle or an aluminum canister. Moreover, the Office alleges that the preferred propellants include HFA 134 and HFA 227, or a mixture thereof. Applicants respectfully disagree.

A claim is anticipated only if each and every element of the claim is described, either expressly or inherently, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). Amended claim 29 requires an "inert non-metal interior surface." Blondino et al. does not disclose an inert non-metal interior surface. At most, Blondino et al. discloses "a plastic coated glass bottle or

an aluminum canister" but does not require that the plastic coat be inert. Col. 3, lines 66-67; *see also* Col. 4, lines 19-20. Nothing in Blondino et al. teaches or suggests an "inert non-metal interior surface" and therefore, does not anticipate the claims. Additionally, as to glass containers, the present application discloses the use of glass containing metal oxide, which may be reactive. *See* page 10, lines 20-29. Accordingly, withdrawal of the rejection is respectfully requested.

35 U.S.C. § 103(a)

Blondino et al. in view of Ercoli et al.

Claims 30 and 32-33 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Blondino et al. (U.S. Patent No. 6,290,930) in view of Ercoli et al. (U.S. Patent No. 3,755,302). The Office acknowledges that Blondino et al. "lacks specific disclosure on other suitable 20-ketosteroid drugs other than budenoside." Office Action at p. 3. The Office therefore combines Ercoli et al., which allegedly teaches a "process for the production of 17-monosters of 17α, 21-dihydroxy-20-ketosteroids," which allegedly include dexamethasone and betamethasone. *Id.* The Office alleges that it would have been obvious "to have looked in the art for other suitable steroids because preparing more stable solution formulations for aerosol delivery with other active agents would provide patients and health care providers with more options and better therapeutic outcomes." *Id.* Applicants respectfully disagree.

As noted above, Blondino et al. fails to teach or suggest an "inert non-metal interior surface." Ercoli et al. does not make up for this deficiency. Ercoli et al. teaches certain steroids and a process for making them but does not teach any container for a

medicinal aerosol steroid solution formulation. Accordingly, Blondino et al. in view of Ercoli et al. does not make the claimed invention obvious. Withdrawal of the rejection is respectfully requested.

Ashurst et al. in view of Saidi et al.

Claims 29-31 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Ashurst et al. (U.S. Patent No. 6,131,566) in view of Saidi et al. (U.S. Patent No. 6,241,969). The Office alleges that Ashurst et al. teaches a metered dose inhaler having part or all of its internal metallic surfaces coated with one or more fluorocarbon polymers in combination with one or more non-fluorcarbon polymers. Office Action at p. 4. The Office further alleges that the preferred drug formulations contain salmeterol in combination with anti-inflammatory steroid such as fluticasone, beclomethasone, budesonide, and triamcinolone acetonide, and propellants such as HFA 134a and HFA 227. *Id.* Furthermore, the Office alleges that the MDI cans and caps may be fabricated from glass or plastic and that the internal surface of the inhaler can be coated by a fluorocarbon polymer. *Id.* The Office, however, admits that "Ashurst et al's formulations are in suspension form and lacks specific disclosure on solutions." *Id.*

Thus, the Office combines Saidi et al., which allegedly teaches "compositions containing corticosteroids in a dissolved state" and that the corticosteroids include betamethasone, budesonide, triamcinolone, dexamethasone, dexamethasone 21-isonicotinate. *Id.* The Office alleges that it would have been obvious "to have looked in the art for other dosage forms of the formulation such as solutions as taught by Saidi et

al. with the reasonable expectation of successfully preparing a formulation that is stable, effective and easy to administer." Office Action at p. 5. Applicants respectfully disagree.

The instant claims are directed to a "medicinal aerosol steroid solution formulation metered dose inhaler product with enhanced chemical stability" including an aerosol container "provided with an inert non-metal interior surface so as to reduce chemical degradation of the 20-ketosteroid." As the Office acknowledged, Ashurst et al. is directed to aerosol ***suspension*** compositions, not to solution formulations as claimed. Moreover, the suspension compositions of Ashurst et al. are also specifically directed to ***albuterol***, which is not a 20-ketosteroid. Even when albuterol may be combined with other medicaments such as anti-inflammatories, Ashurst et al. provides that the formulation in their metered dose inhalers (MDIs) must be in suspension:

> the drug formulation for use in the invention may, if desired, contain albuterol or a salt thereof . . . in combination with one or more other pharmacologically active agents . . . It will be clear to a person skilled in the art that, where appropriate, the medicaments may be used in the form of salts . . . or as esters . . . or as solvates . . . to optimise the activity and/or stability of the medicament and/or ***to minimise the solubility of the medicament in the propellant***.

Col. 3, lines 19-51 (emphasis added). Indeed, all 42 examples in Ashurst et al. exemplify suspension formulations of albuterol, not solution formulations. Also noteworthy is the fact that none of these examples provide albuterol in combination with any other medicament.

Moreover, the concern for Ashurst et al. appears to be albuterol adhering the inner surfaces of the can, valves, and caps of metered dose inhalers (MDIs). Ashurst et al. states that:

> We have found that coating the interior can surfaces of MDI's with a fluorocarbon polymer significantly reduces or essentially eliminates the problem of adhesion or deposition of ***albuterol*** on the can walls and thus ensures consistent delivery of medication in aerosol from the MDI.

Col. 1, lines 59-63 (emphasis added). Thus, the coating was provided to specifically prevent albuterol from sticking to the surface of the MDIs, NOT to increase stability of albuterol. Ashurst et al. does not show or even recognize that this coating could increase the stability of 20-ketosteroids. In fact, as noted above, none of the 42 examples shown in Ashurst et al. even test other medicaments in the coated MDIs, other than albuterol. Therefore, nothing in Ashurst et al. teaches or suggests that the suspension formulations containing albuterol could be replaced with a solution formulation containing 20-ketosteroids and that the stability of 20-ketosteroids could be increased by coating the inner surface of MDIs.

Saidi et al. fails to make up for the deficiencies of Ashurst et al. Saidi et al. utilizes a completely different system from Ashurst et al. for delivering a medicament directly into the lungs or nasal passage. Saidi et al. provides solution formulations of corticosteroids for use in ***nebulizers***, not in MDIs. As Saidi et al. explains, propulsion in MDIs is "accomplished by use of pressurized gas or by any of a variety of mechanical means of entraining a fine powder into a gas or air stream." Col. 1, lines 34-36. With MDIs, "once the therapeutic drug leaves the device, it is, or becomes, ***a fine powder***." Col. 1, lines 39-41 (emphasis added). In contrast, nebulizers "work by means of an air

jet or an ultrasonic pulse that is applied to a solution producing ***a fine mist***." Col. 2, lines 4-6 (emphasis added). The differences in the propulsion mechanisms designed to produce different end products, as well as the differences in the drugs being used by Ashurst et al. and Saidi et al., suggest that there is no reasonable expectation of success that a solution formulation designed specifically for corticosteroids for use in a nebulizer will work and deliver appropriate amounts of that drug from an MDI that has been developed for use in delivering albuterol suspension formulations.

In fact, Saidi et al. teaches away from the use of MDIs for solution formulations. Saidi et al. explains that water-insoluble drugs, such as corticosteroids, "have usually been formulated as ***suspensions*** of micronized drug powder . . . and delivered by metered dose inhaler . . . [because of] the fact that coritcosteroids are very difficult to stabilize in aqueous media and frequently produce systems that exhibit crystal growth, precipitation, and/or aggregation of suspended or solubilized drug." Col. 3, line 66 to col. 4, line 7 (emphasis added). Moreover, Saidi et al. suggests that MDIs are not ideal:

> Additional considerations for the use of powder-type drug delivery devices for inhalation include the limited amount of drug that can be contained in one or two puffs from the device and the need for the user to skillfully coordinate hand activation of the device with inhalation. This latter limitation is particularly important for those patients who are disabled, children, or elderly.

Col. 1, line 63 to col. 2, line 2. In contrast, with nebulizers,:

> it is possible to rebreathe a portion of the mist during several minutes of treatment and increase the capture of the fine droplet fraction that can penetrate the lung most deeply. In addition, there is no need for coordination between hand action and breathing, making the nebulizer easier to use for patients.

Col. 2, lines 12-17.

Thus, Saidi et al. set out to prepare a solution formulation of corticosteroids for use with nebulizers. These solution compositions of corticosteroids contained from about 0.1 to about 20 percent by weight of a high-HLB (hydrophilic-lipophilic balance) surfactant component of greater than about 10 and at least 70 weight percent of an aqueous phase. When tested in a nebulizer, the nebulized corticosteroid compositions exhibited a mass median aerodynamic diameter (MMAD) below 5 micrometers but greater than 0.5 micrometers, a size range suitable for a drug to enter into the lungs without being captured in the nasal passage and swallowed. *See* Example 5; *see also* col. 1, lines 47-62.

Significantly, Saidi et al. did NOT test these solution compositions in MDIs. And, as noted above, Ashurst et al. did not test any solution formulation in MDIs and did not test any drug other than albuterol. Therefore, there would have been no reasonable expectation of success that the solution formulations of Saidi et al. would have also worked in MDIs.

There was also no motivation for one skilled in the art to replace the suspension formulation of Ashurst et al. used in the coated MDI, with the solution formulation of Saidi et al. Saidi et al. tested for the stability of the corticosteroid solution compositions and found that:

> From these data it can be concluded that the tested formulations are ***physically stable***, meaning that there was ***no phase separation or precipitation*** of the drug under stressed conditions. ***No degradation of the corticosteroid was observed.***

Col. 12, lines 23-27 (emphasis added). Because the corticosteroid showed complete solubility and physical stability, there would have been no motivation to provide the coating of Ashurst et al.

Accordingly, Applicants assert that the claims are not obvious in view of Ashurst et al. and Saidi et al. Withdrawal of the rejection is respectfully requested.

Ashurst et al. in view of Saidi et al. and further in view of Williams et al.

Claims 34-37 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Ashurst et al. (U.S. Patent No. 6,131,566) in view of Saidi et al. (U.S. Patent No. 6,241,969) as applied to claims 29-31 above, and further in view of Williams et al., *European J. of Pharmaceutics and Biopharmaceutics* 44:195-203 (1997). The Office acknowledges that the "combination of Ashurst et al. and Saidi et al., discussed above, lacks specific disclosure on the specifics of coatings as claimed in claims 34-37." However, the Office alleges that Williams et al. discloses a drug "formulated in a canister as a suspension or solution dispersed in a propellant, typically HFAs," and that the "stability of the formulation and the accuracy of the emitted dose are influenced by formulation composition and the choice of the material composition of the delivery device." Office Action at p. 6. The Office further alleges that "materials such as glass, aluminum and tin plates are used to manufacture pDMIs" and that "the internal surface of the container is lined with an inert organic coating." *Id.* Thus, the Office concludes that "[i]t would have been obvious to one of ordinary skill in the art at the time the invention was made to have combined the references because the design incentives or market forces provided a reason to make an adaptation, and the invention resulted from

application of the prior knowledge in a predictable manner." *Id.* Applicants respectfully disagree.

Williams et al. does not make up for the deficiencies of Ashurst et al. and Saidi et al. discussed above. Williams et al. is simply a study of the effects of propellants, HFA 134a and HFA 227, on the specific coatings. Williams et al. did not test any drug whatsoever and no suspension formulation or solution formulation was tested by Williams et al. Moreover, Williams et al. suggests that the use of different formulations, medicament, and device may produce different results:

> The stability of the formulation and the accuracy of the emitted dose are influenced by formulation composition and the choice of the material composition of the delivery device.

Page 195, col. 2. Thus, it would not have been obvious to combine the teachings of Ashurst et al., Saidi et al. and Williams et al. with a reasonable expectation of success. Accordingly, withdrawal of the rejection is respectfully requested.

Obviousness-type double patenting

Claims 29-37 are provisionally rejected for obviousness-type double patenting as allegedly being unpatenable over claims 29-37 of copending Application No. 11/061,529 (US App. Pub. No. 20050220717). Applicants enclose a terminal disclaimer that disclaims the terminal part of the statutory term of any patent granted on the instant application that would extend beyond the expiration date of the full statutory term of a patent that may issue from U.S. App. No. 11/061,52. 9. The filing of the terminal disclaimers is not an admission that the claimed invention is unpatentable in view of the

claimed subject matter in the reference application. Applicants respectfully request the withdrawal of the rejection.

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this amendment and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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Dated: March 18, 2008

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